APR 11 2000

NDA 18-163/S-48

Novartis Pharmaceuticals Corporation
Attention: Robert W. Kowalski, Pharm.D
Associate Director
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Dr. Kowaiski:

Please refer to your supplemental new drug application dated May 16, 1995, received May 18, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Restoril® (temazepam) Capsules, USP.

This "Changes Being Effected" supplemental new drug application provides for the following:

- New updated OVERDOSAGE section identifying flumazenil (Romazicon®) as a potentially useful adjunct in the management of benzodiazepine overdose.
- Editorial changes to the DESCRIPTION and the HOW SUPPLIED section.
- An update to include the USP designation throughout the labeling.
- Updated trade labeling, including changes to the "logo" and "artwork", which introduces the "Landor" design.

We have completed the review of this supplemental new drug application, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on May 16, 1995.

Accordingly, the supplemental new drug application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Ms. Melaine Shin, R.Ph., Regulatory Management Officer. at (301) 594-5511.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

OVERDOSAGE

Manifestations of acute overdosage of Restoril® (temazepam) can be expected to reflect the CNS effects of the drug and include somnolence. confusion, and coma, with reduced or absent reflexes, respiratory depression, and hypotension. The oral LD50 of Restoril® (temazepam) was 1963 mg/kg in mice, 1833 mg/kg in rats, and>2400 mg/kg in rabbits.

Treatment

If the patient is conscious, vomiting should be induced mechanically or with emetics. Gastric lavage should be employed utilizing concurrently a cuffed endotracheal tube if the patient is unconscious to prevent aspiration and pulmonary complications. Maintenance of adequate pulmonary ventilation is essential. The use of pressor agents intravenously may be necessary to combat hypotension. Fluids should be administered intravenously to encourage diuresis. The value of dialysis has not been determined. If excitation occurs, barbiturates should not be used. It should be borne in mind that multiple agents may have been ingested. Flumazenil (Romazicon®)*, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS. and PRECAUTIONS should be consulted prior to use.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference.

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*Romazicon is the registered trademark of Roche Laboratories.